Aging Research Update: Improving the Health and Quality of Life of America's Seniors

Meeting with the Friends of NIA

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Director
National Institute on Aging

March 22, 2013

NIA Cutting Edge Research

- Clinical trials to improve and maintain physical function of older men and women
- Understanding the basics of aging and translating from animal models to human studies
- Better understanding of U.S. health and well-being to guide research and policy
- Building the Genetic Infrastructure of Diseases of Aging
- National Alzheimer's Project Act - Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025

Testosterone Trial

- Objectives: determine whether testosterone treatment of elderly men with low serum testosterone concentrations, symptoms and measured abnormalities in physical or sexual function, vitality, cognition, and anemia will result in more favorable changes in those abnormalities than placebo treatment
- Design: randomized, placebo-controlled, double-blind study of seven coordinated trials in men ages 65 years and older
- Recruitment completed, results are expected in 2015

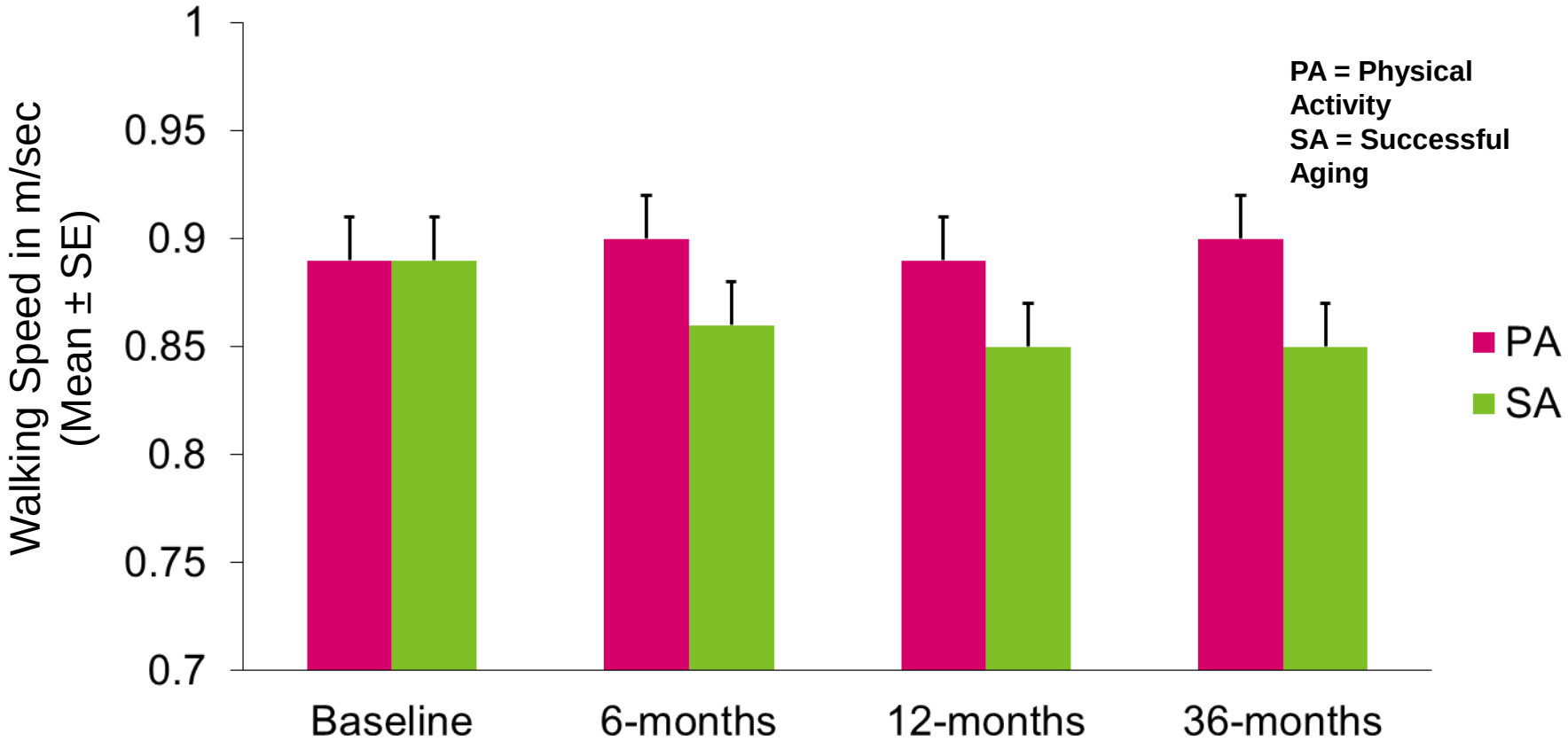
THE T TRIAL
THE TESTOSTERONE TRIAL

Testosterone Trial – *Outcomes*

- **Physical Function Trial** - proportion of men improving their six-minute walking distance by >50 meters
- **Sexual Function Trial** - improvement in sexual activity, as assessed by the Harbor-UCLA 7-day Sexual Function Questionnaire
- **Vitality Trial** – proportion of men who have an improvement of ≥4 points on the FACIT-Fatigue scale
- **Cognitive Function Trial** - improvement, or less decline, in verbal memory as assessed by Wechsler Memory Scale
- **Anemia Trial** - proportion of men whose anemia is corrected
- **Cardiovascular Trial** - Change in atherosclerotic plaque burden as assessed by cardiac CT angiography
- **Bone Trial** - increase in volumetric trabecular bone mineral density (vBMD) of the lumbar spine as measured by quantitative computed tomography (QCT)

THE T TRIAL
THE TESTOSTERONE TRIAL

2-Year Follow-up of Life Pilot Participants



Source: J Gerontol A Biol Sci Med Sci 2009

LIFE Study

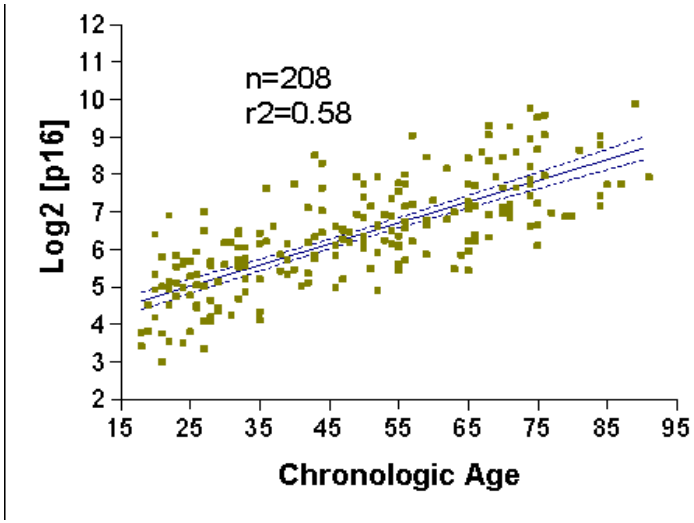
- Objective: obtain definitive evidence regarding whether exercise can prevent the onset of major mobility disability
- Design: multicenter randomized trial comparing physical activity to successful aging intervention in community-dwelling individuals 70-89 years of age
- 1635 participants were enrolled and are currently followed
- Results will be published in 2014
- Outcomes:
  - ✓ Primary - major mobility disability defined as inability to walk 400 meters
  - ✓ Secondary – cognitive function, serious fall injuries, disability in activities of daily living

THE LIFE STUDY

A Cell Senescence Marker for Aging (p16^{ink4a})

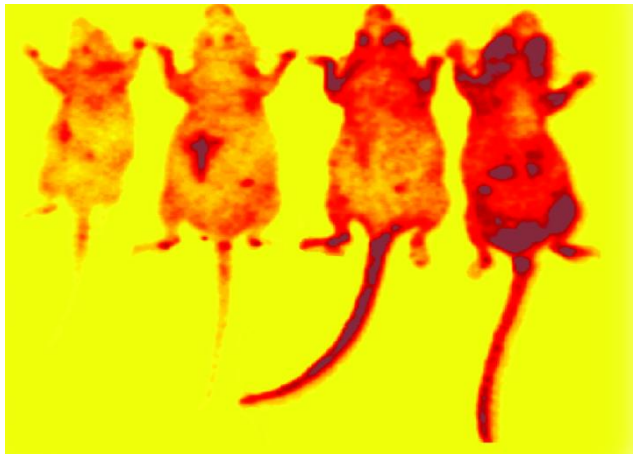
Sharpless lab, University of North Carolina

In Humans p16^{ink4}a expression in CD3+ T cells)



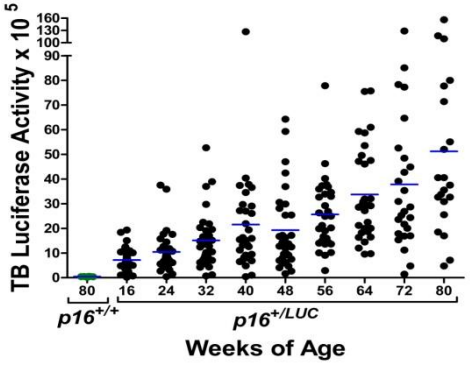
- **increases 1.4-fold per decade => 16-fold over 8 decade adult lifespan.**
- **Increase seen well before 'aging' is apparent.**

In Mice, a reporter of p16^{ink4} expression in all cells of the body



16 40 64 80

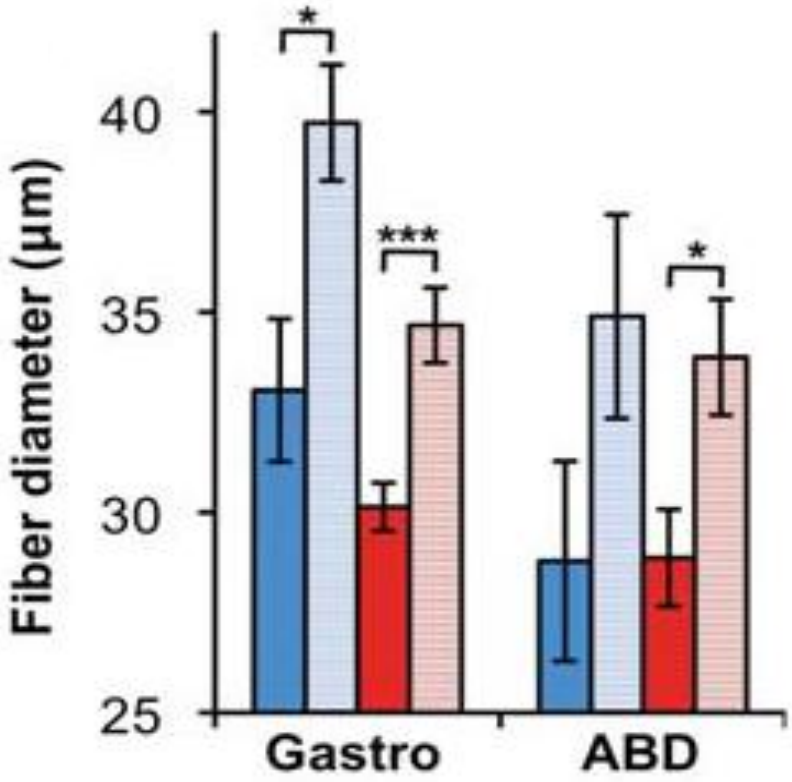
Weeks of age (one mouse)

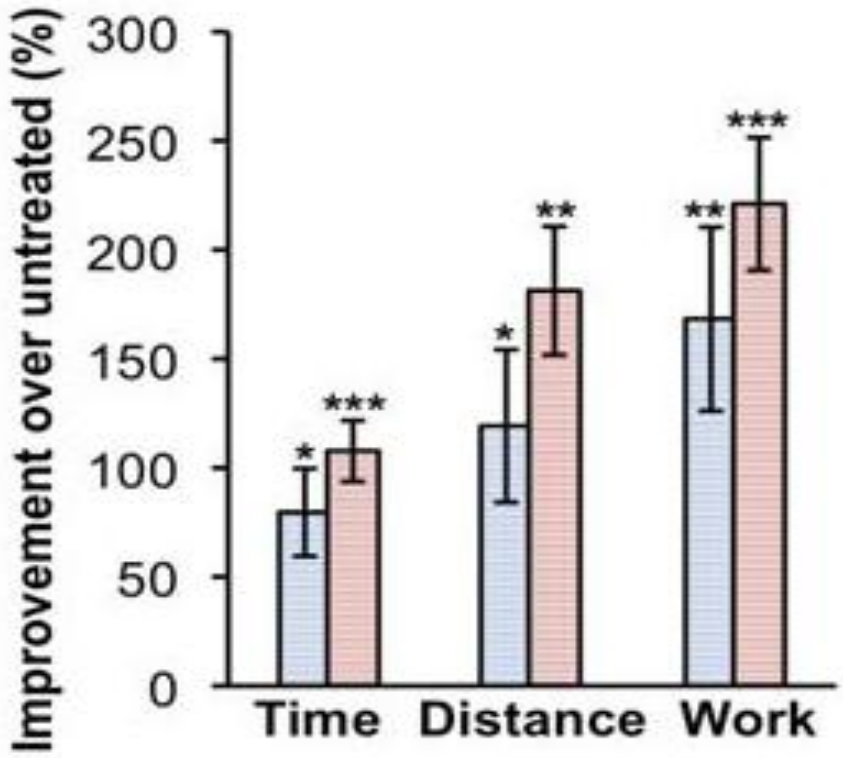


(many mice)

Adapted from
Liu et al Aging Cell 8:439-448 (2009) – human studies
Burd et al. Cell 152: 340-351 (2013) – C57BL6 mouse model

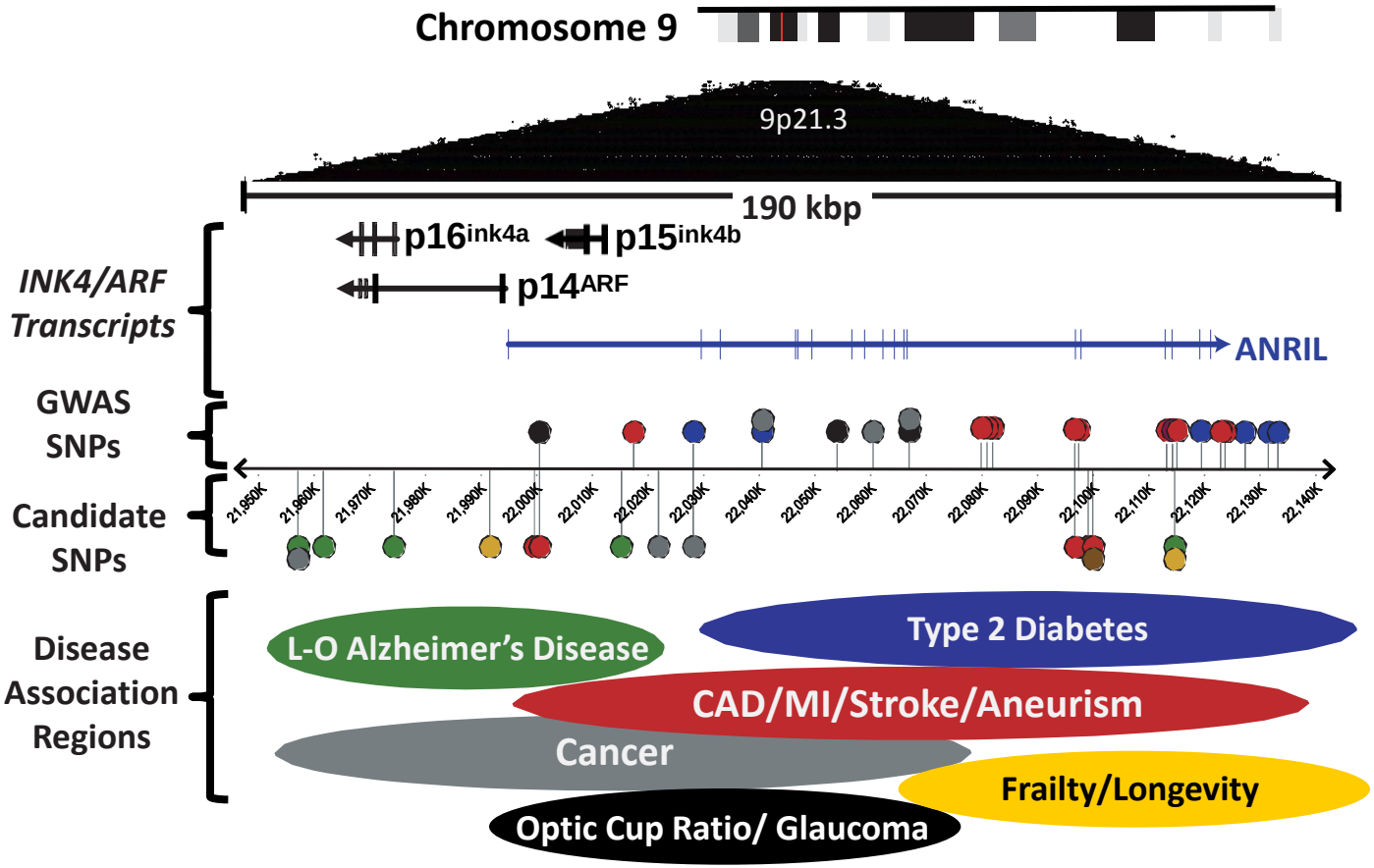
Removal of p16^{Ink4a}-positive Senescent Cells in Transgenic Mice Delays Ageing-Associated Disorders





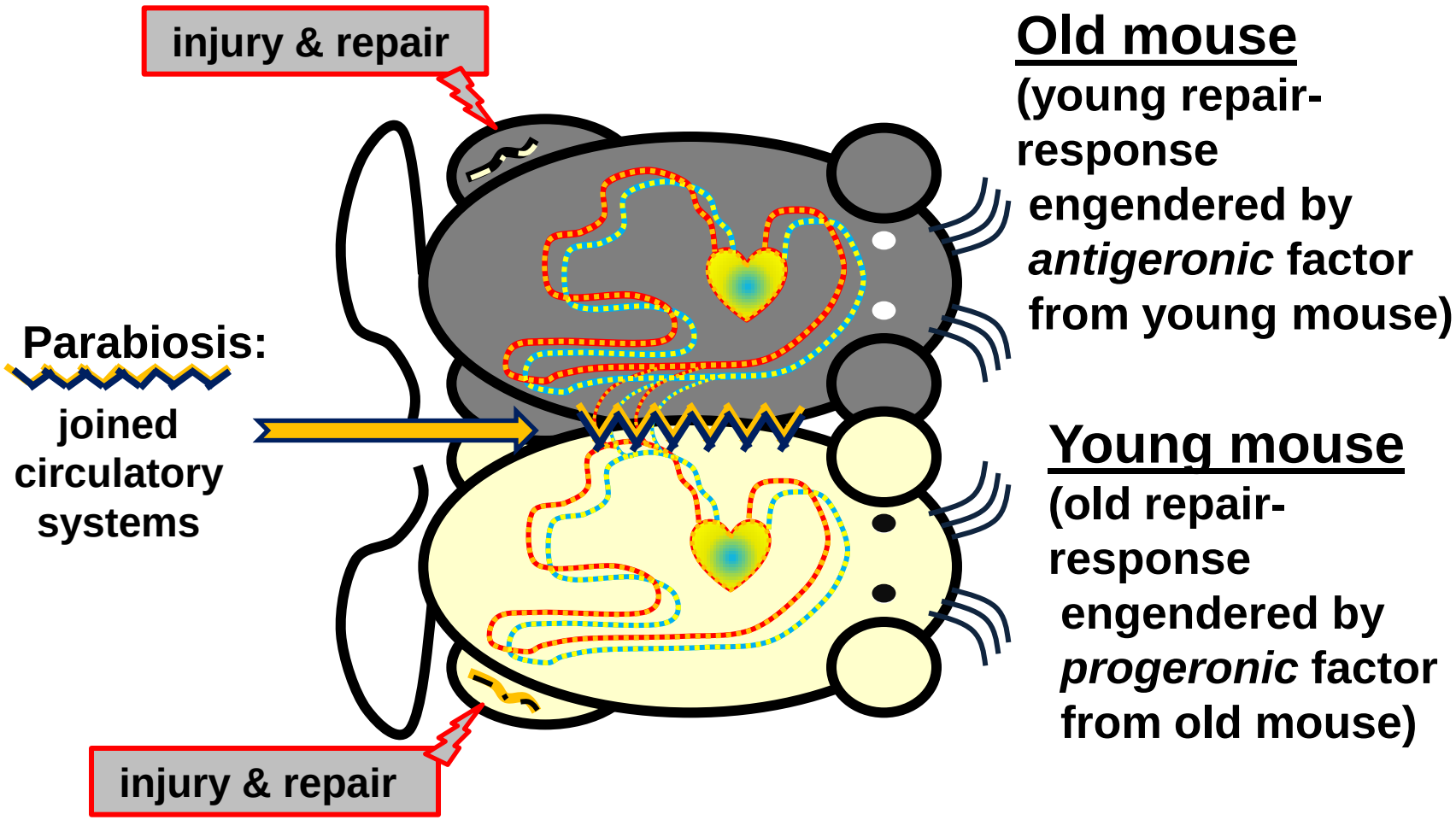
Baker *et al.*
Nature 2011

SNPs for Aging Related Diseases Clustered Near the p^{16ink4a} Locus



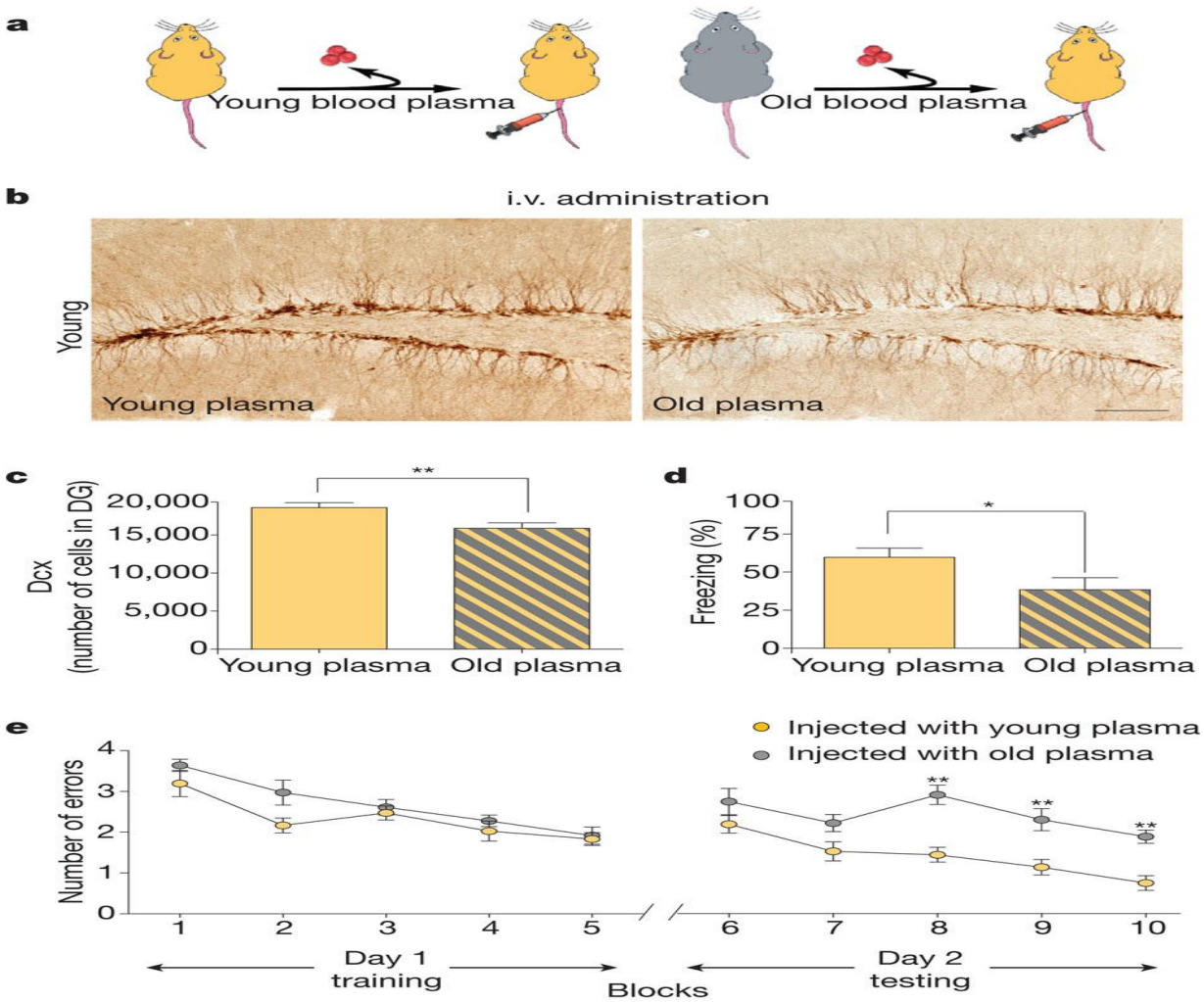
modified from Jeck, Siebold & Sharpless (2012) *Aging Cell*

Heterochronic Parabiosis: Age-Reciprocal Outcomes for "Aging Factors"



Courtesy of Dr. Ron Kohanski, NIA (2011)

Factors from an Old Systemic Environment Decrease Neurogenesis and Impair Learning and Memory



SA Villeda *et al*. *Nature* 477, 90-94 (2011)

NIH Geroscience Interest Group (GSIG)

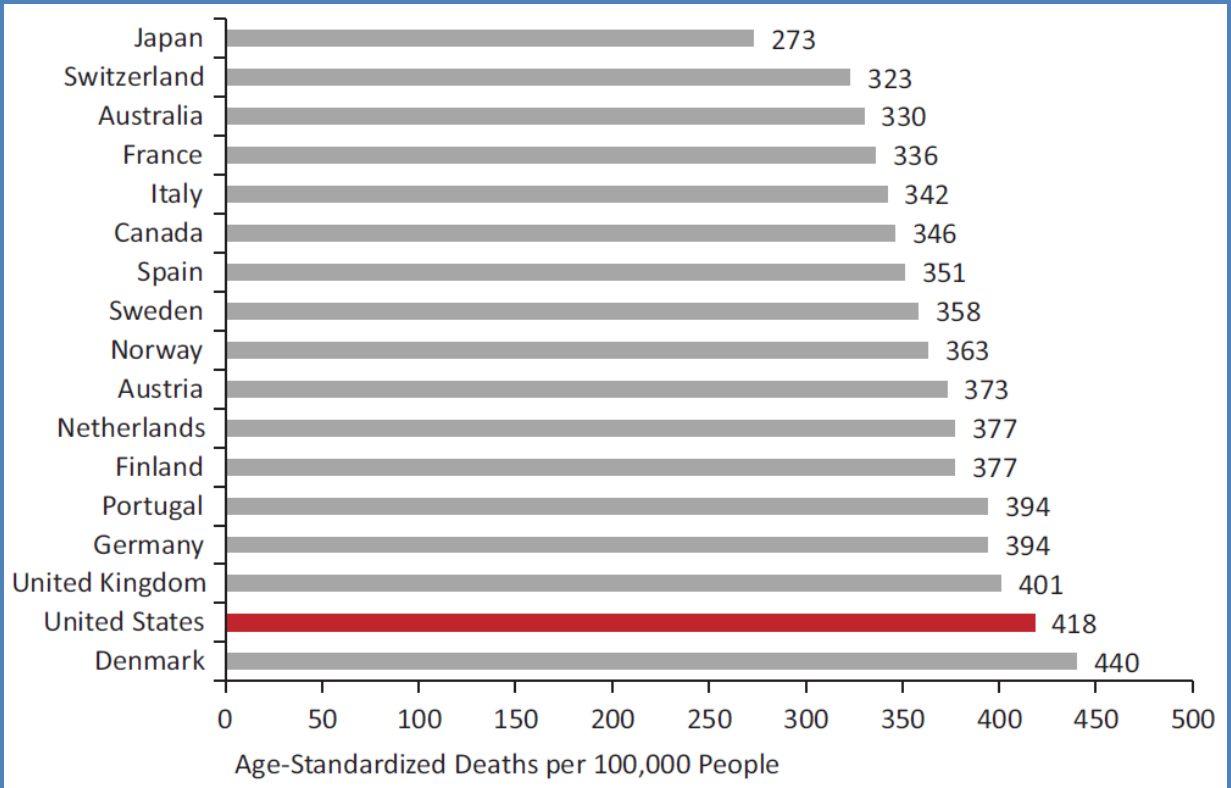
Trans-NIH organization of 20 Institutes initiated by NIA to:

- Raise awareness of the relevant role played by aging biology in the development of diseases and disabilities.

- Promote discussion and co-funding of initiatives across the NIH, based on the above.

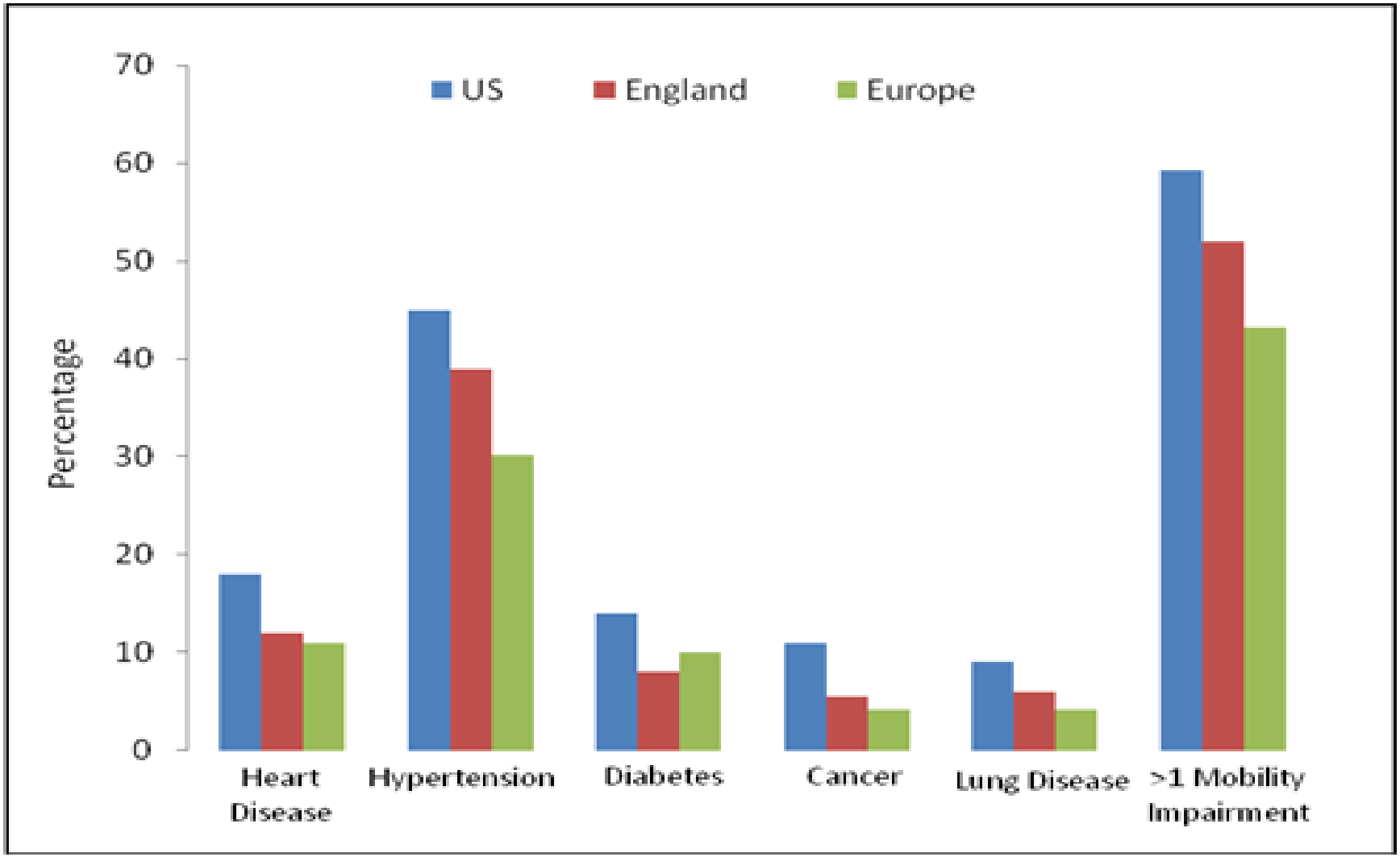
http://sigs.nih.gov/geroscience/Pages/default.aspx

Mortality from Non-Communicable Diseases (NCD), 2008



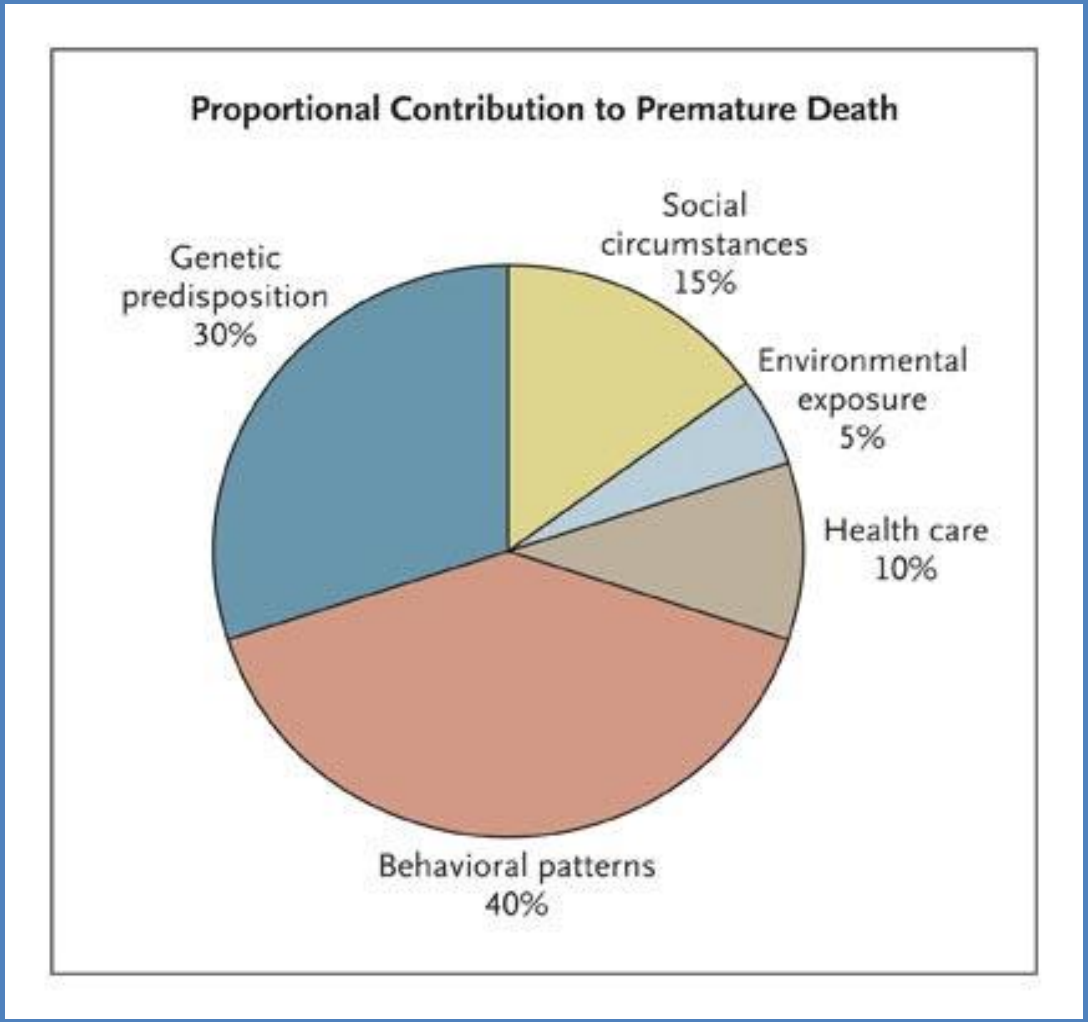
Among the 17 peer countries, the US had 2nd highest NCD mortality rate in 2008 (418:100,000)

Prevalence of Chronic Disease and Disability among People Aged 50-74 in the US, England, and 10 Other European Nations: 2004



Source: Adapted from Avendano, Glymour, Banks, and Mackenbach, AJPH, 2009.

Determinants of Health and Their Contribution to Premature Death



Schroeder SA. N Engl J Med 2007;357:1221-1228.

The NEW ENGLAND JOURNAL of MEDICINE

Reversibility of Early Disadvantage

David Reiss (*Yale*, BSR Contractor)
Steve Suomi (*NICHD*)
Richard Suzman, Lis Nielsen and Jonathan King (BSR Staff)

- **Early Disadvantage:** Human and animal studies document long lasting effects of adverse early environments on trajectories of physical and psychological aging
  - **Low socioeconomic status** → Increased risk for coronary heart disease (Kittleson et al., 2006)
  - **Adverse parent-offspring relationships** → Heightened physiological stress response (Lui & Meaney, 1997)
  - **Early social deprivation/stress** → Heightened risk of illness in midlife (Danese & Moffitt, 2009; Conti et al., 2012)
- **Potential for Intervention:** Evidence emerging that underlying risk mechanisms are reversible, suggesting possibility of intervention.
- **Research Agenda:**
  - ***Identifying Biobehavioral Risk Mechanisms:*** *What accounts for the persistent effect of childhood environmental adversity on trajectories of aging?*
  - ***Developing Novel Strategies for Reversing Risk:*** *What promising behavioral interventions in midlife can reverse this risk? What is their impact on these biobehavioral mechanisms?*

Does Medicaid Improve the Health and Well-Being of the Poor?

- The Oregon Health Plan (Medicaid) held a lottery to add beneficiaries creating random assignment to treatment group (Medicaid) versus controls (not enrolled in Medicaid) to consider the impact of health insurance on health.

- In the year after random assignment, the treatment group is:
  - about 25 percentage points more likely to have insurance
  - significantly higher health care utilization (including primary and preventive care as well as hospitalizations)
  - lower out-of-pocket medical expenditures and medical debt (including fewer bills sent to collection)
  - better self-reported physical and mental health

- Future work will make use of biomarker and administrative data to track health and utilization across both groups.

Source: Baicker, K. and A. Finkelstein (2011), *The New England Journal of Med*

Does Moving to a Lower Poverty Neighborhood Improve Health and Well-Being?

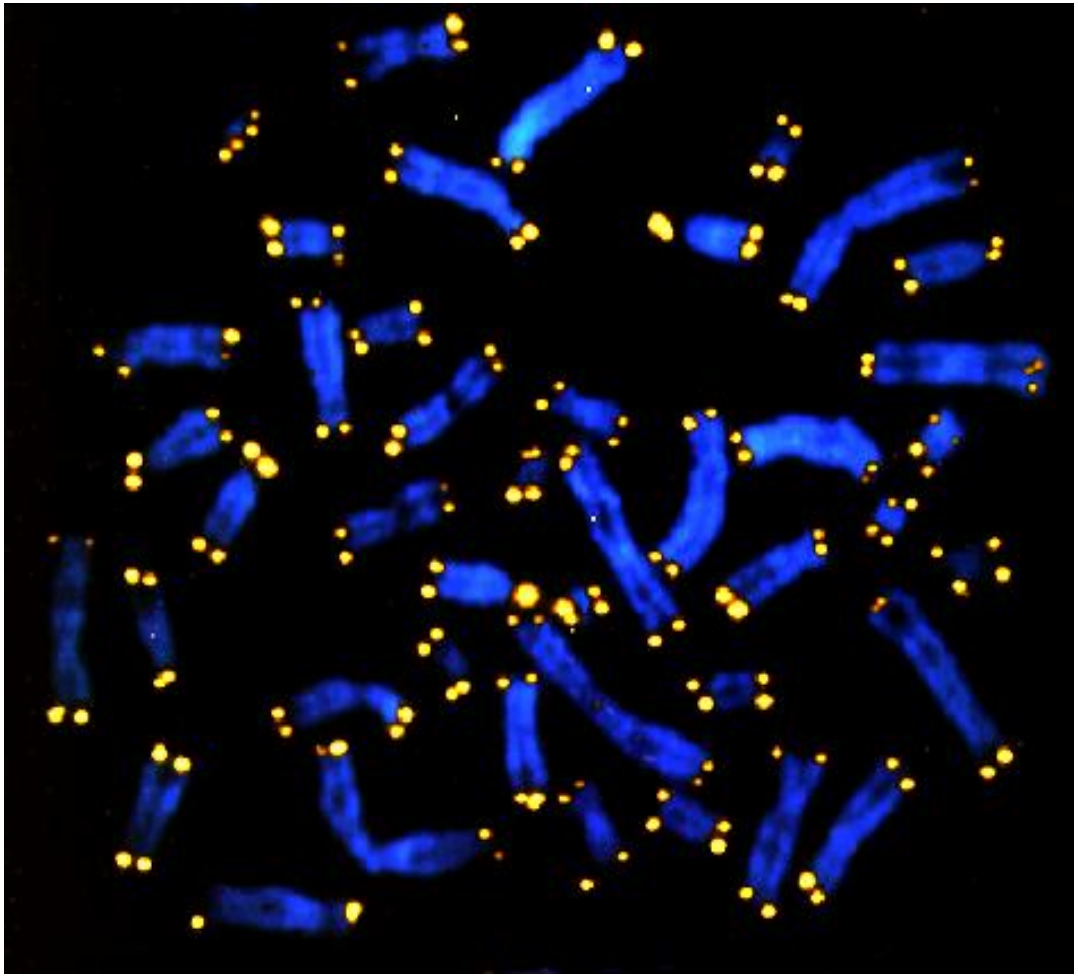
- Moving to Opportunity (MTO) experiment included a treatment for a low-poverty voucher that limited moves to low-poverty Census tracts, a standard housing voucher, and a control group.

- The opportunity to move from a neighborhood with a high level of poverty to one with a lower level of poverty had an effect on glucose control for adults that was comparable to that of metformin.

- Improvements in subjective well-being experienced by MTO respondents (with an average annual income of $20,000) was equivalent to a $13,000 increase in an annual income despite the fact that the treatment did not affect economic self-sufficiency.

Ludwig, J et al. (2011), NEJM 365: 1509-1519.

Telomeres

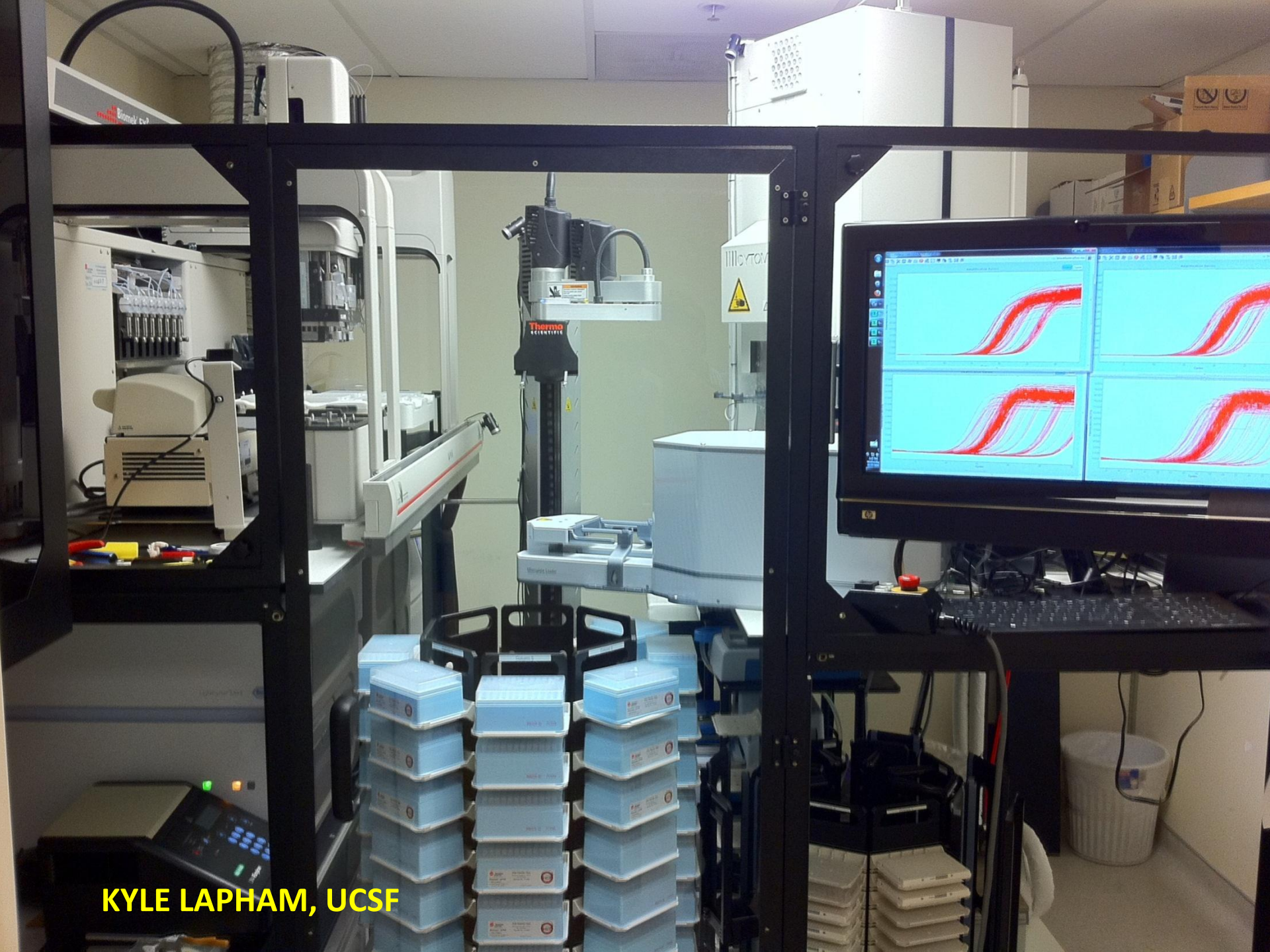


Chromosomal integrity

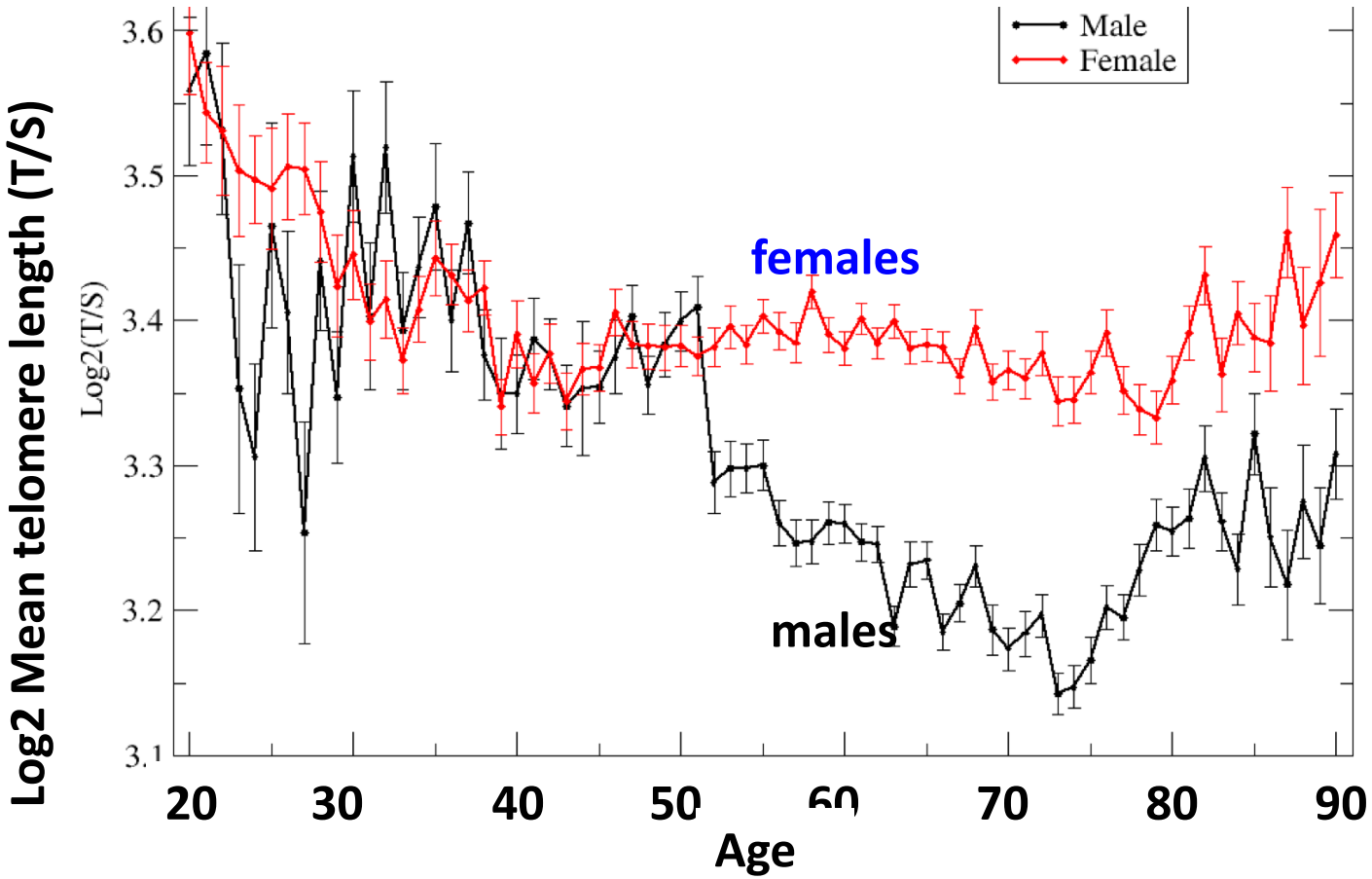
Chromosomal location

Apoptotic resistance

Cell replication capacity

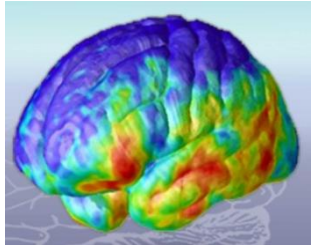

KYLE LAPHAM, UCSF

Mean Human Telomere Length with Age
Males vs Females



Kaiser Permanente Research Program in Genes, Environment and Health (RPGEH) Genetic Epidemiology Research on Aging (GERA) Cohort

Lapham, Kvale, et al, unpubl.



Alzheimer's Research Highlights - Gene Discovery

1991
APOEε4
APP*

1995
PS1*
PS2*

1996
Transgenic Mouse models

2005
First published GWAS

2009
PICALM*
CLU*
CR1*
GWAS

2010
BIN 1*
Five additional genes discovered by GWAS

2011
MS4A4/MS4A6E, CD2AP, SORL1,*
By GWAS
3 others to be confirmed

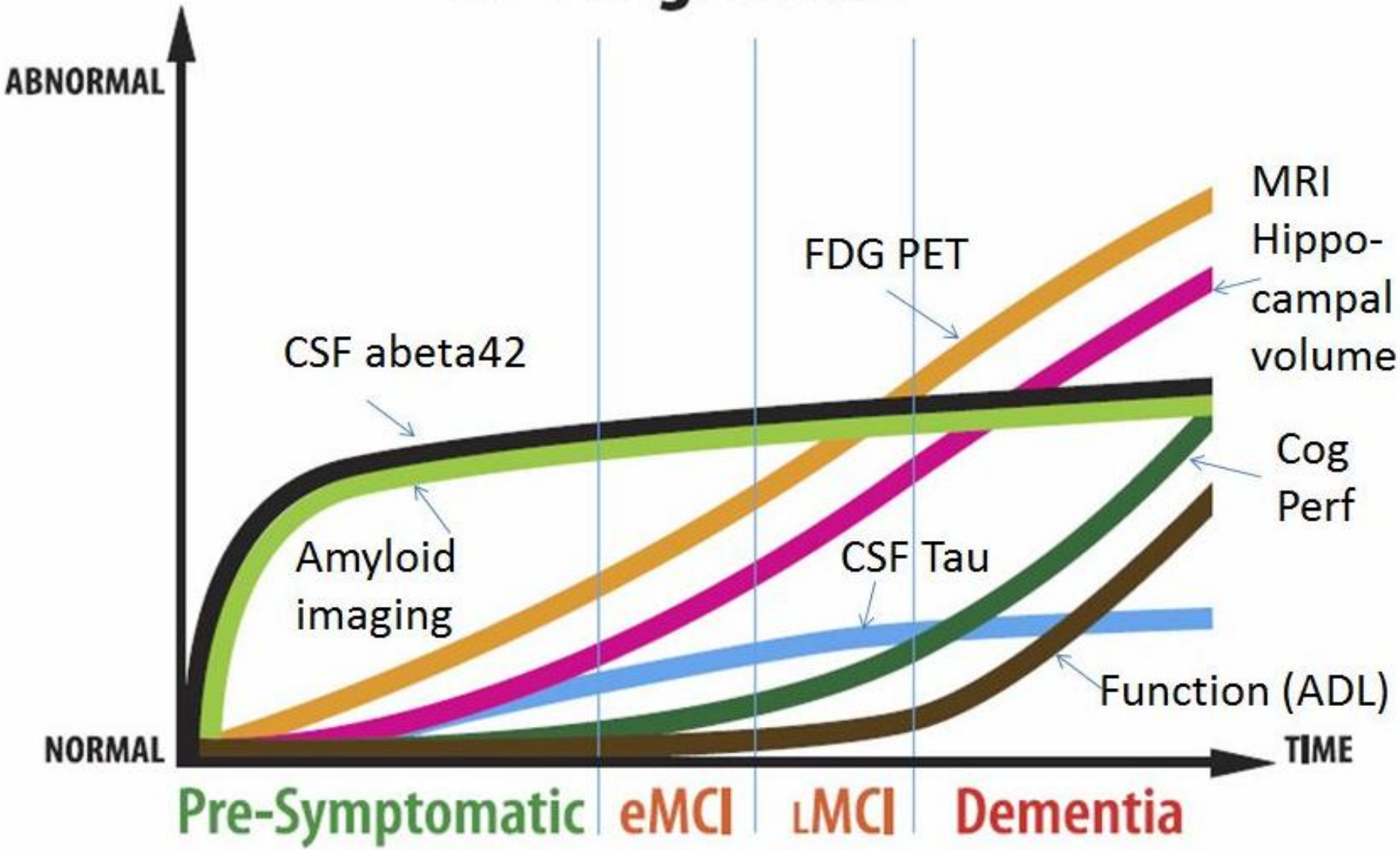
2012
TREM2*

* Early onset Alzheimer's Disease- family based studies

* Late onset Alzheimer's Disease case control and family based studies

Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls

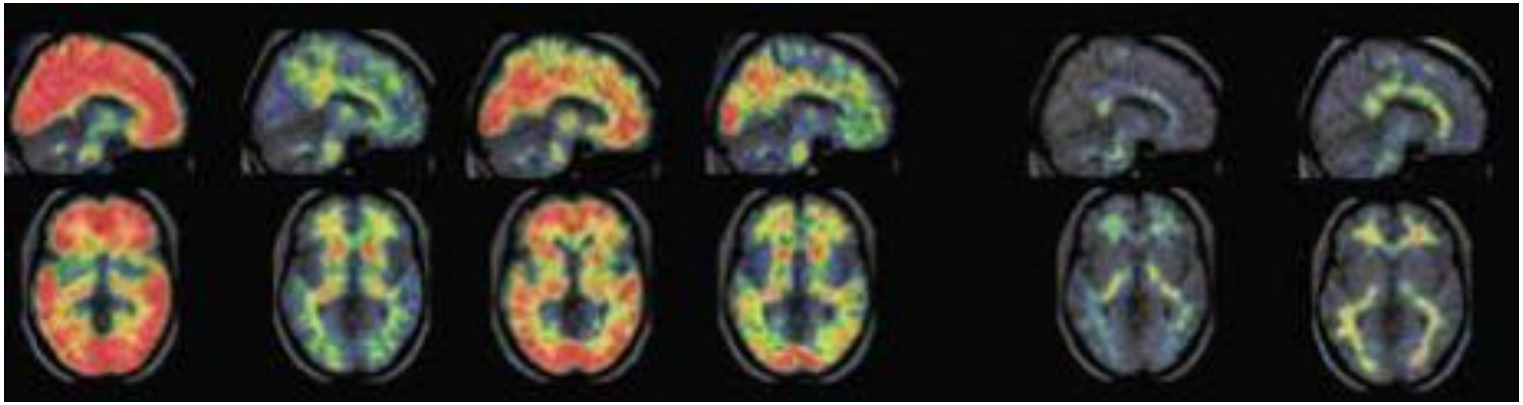
AD Progression



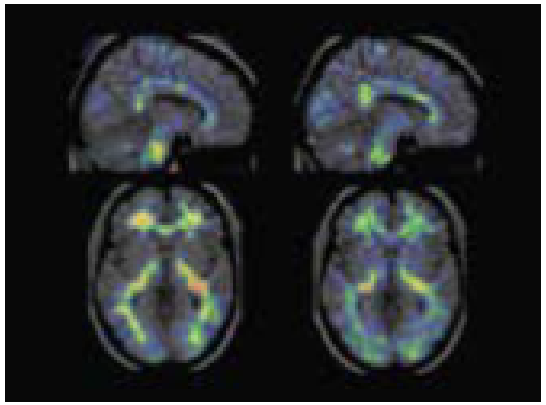
Based on Jack, Lancet Neurol, 2010

Amyloid PET Scans in *Presymptomatic* Early-Onset Alzheimer's Disease

Gene Carriers **Non-Carriers**



Age 35-39 Years



Age 25-29 Years

Colombian Kindred

- N = 5000 living individuals from ~ 25 families
- 1500 with the *E280A (Glu280Ala) Presenilin1* mutation
- Autosomal dominant, 100% penetrance
- Median age of MCI = 44 years, dementia = 49 years

Fleisher, AS, Reiman, E.M .and colleagues (2012). *Lancet Neurology*

Pilot Trial of Intranasal Insulin for Alzheimer's and Mild Cognitive Impairment

Pilot: 104 adults with MCI and mild to moderate Alzheimer's placebo, 20 IU insulin, 40 IU insulin for 4 months, administered with nasal drug delivery device

Results:

- Improved delayed memory in 20 IU group compared with placebo
- Preserved general cognition, activities of daily living for younger participants in both insulin groups
- Caregivers for both insulin groups rated participant functional status higher
- Changes in some biomarkers (Aβ42 and tau to Aβ42 ratio) associated with changes in memory and function

Suzanne Craft et al, Arch Neurol 2012 January; 69(1): 29-38

Understanding Genetic Infrastructure

NIH/NIA Budget Update

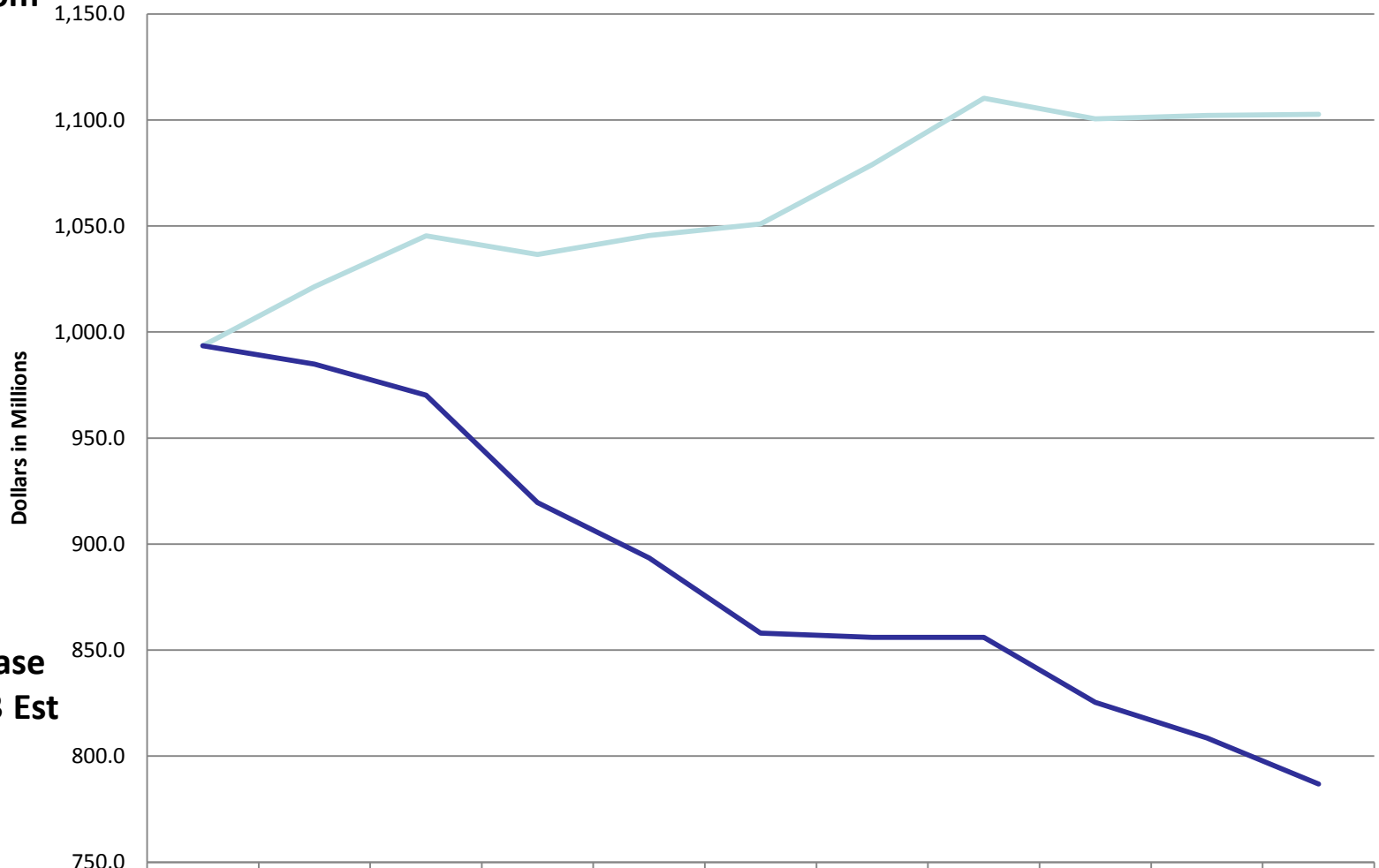
NIA Appropriations - FY12 Enacted, FY13 President's Budget
Current versus Constant, FY03 Base Year

Difference from FY2003

In Current Dollars: $109.1M Increase

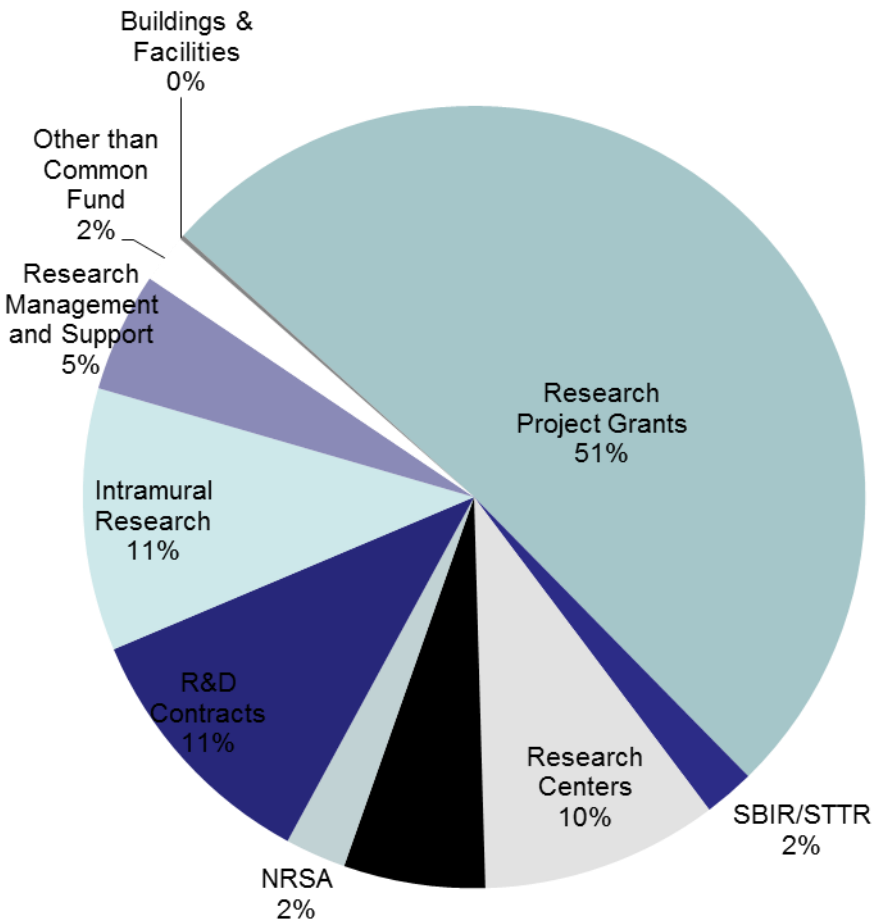
In Constant Dollars: $206.7M Decrease

20.8% decrease FY2003-2013 Est

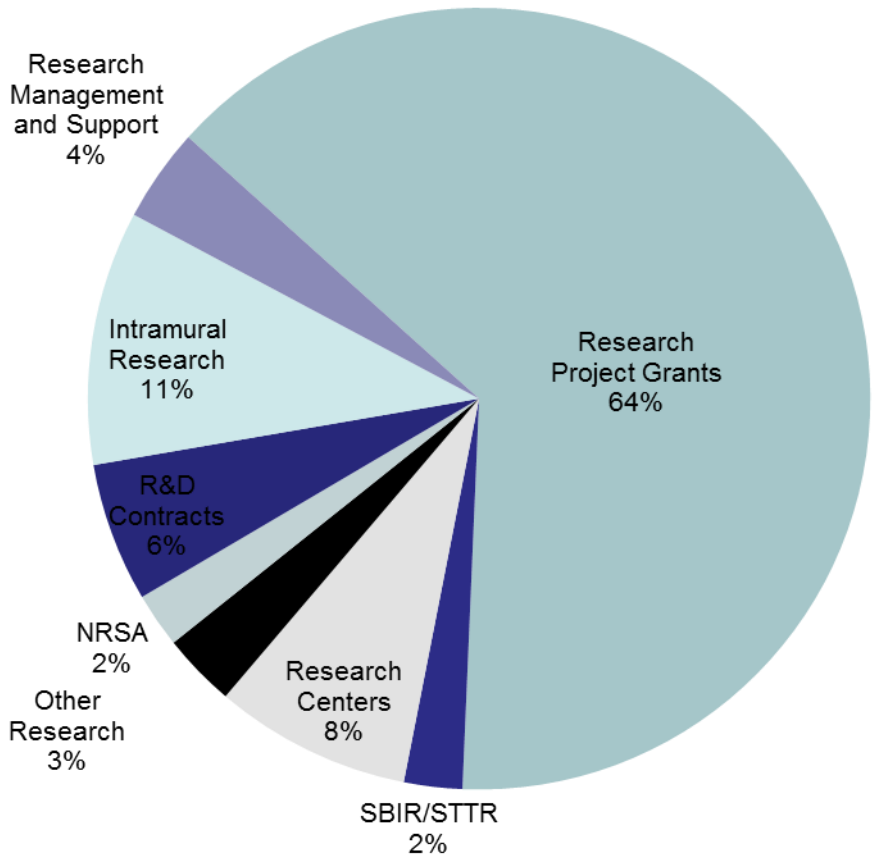


	FY03	FY04	FY05	FY06	FY07	FY08	FY09	FY10	FY11	FY12	FY13 Est
Series1	993.6	1,021.4	1,045.3	1,036.6	1,045.5	1,051.0	1,079.0	1,110.2	1,100.5	1,102.1	1,102.7
Series2	993.6	984.9	970.2	919.5	893.5	858.0	856.1	856.0	825.3	808.6	786.9

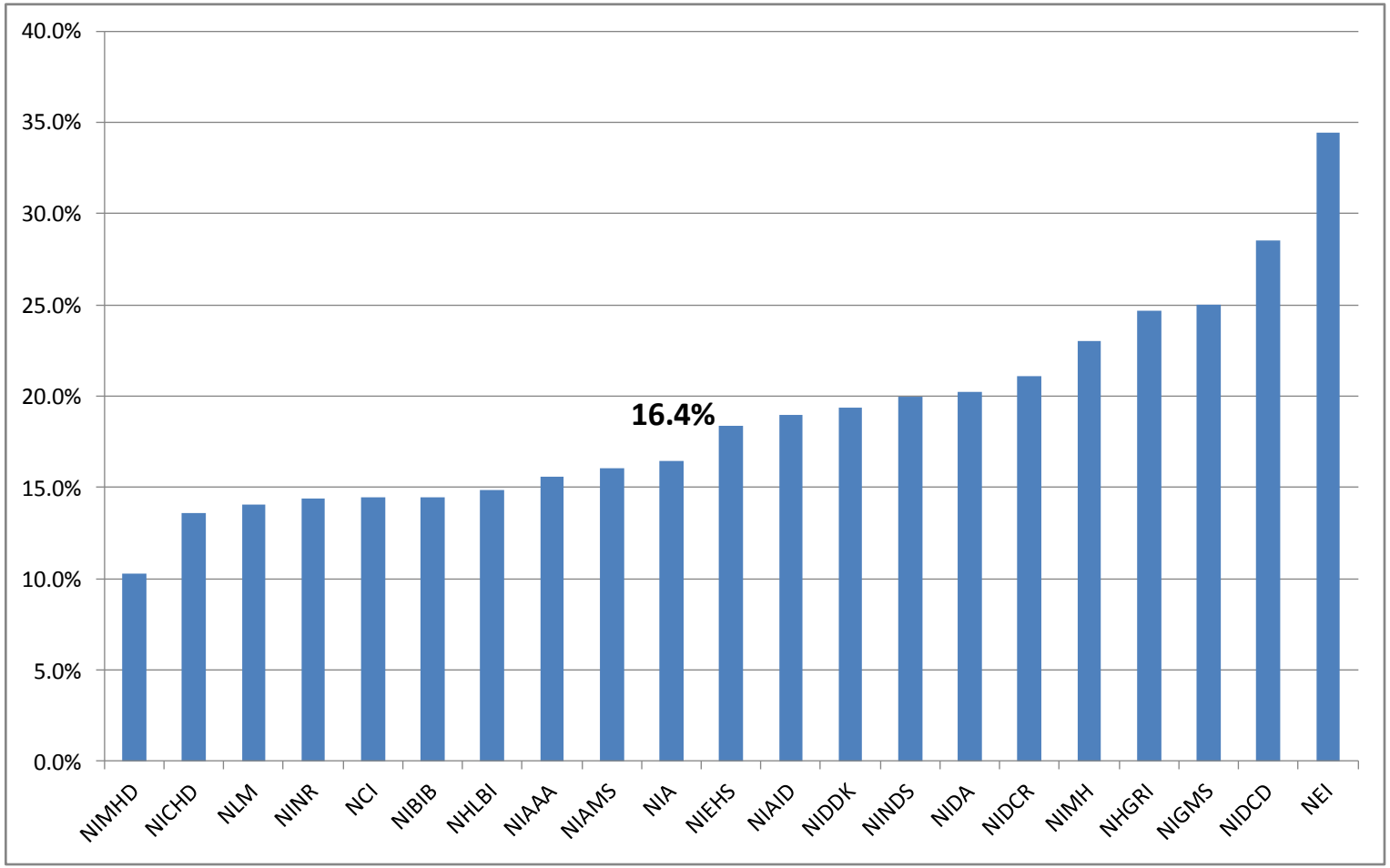
Proportion of Total NIH Budget, FY2011
RPGs are 51%



Proportion of Total NIA Budget, FY2011
RPGs are 64%



NIA and NIH RPG Success Rates 2008 to 2012

	2008	2009	2010	2011	2012
NIH	21.8%	20.6%	20.6%	17.7%	17.6%
NIA	20.4%	17.5%	14.5%	16.1%	15.5%

NIH R01 Success Rates for FY2012